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PATENT

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicants: Achari et al.

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For: PHARMACEUTICAL FORMULATIONS AND METHODS COMPRISING INTRANASAL MORPHINE

Examiner: Oke, V.

Group Art Unit: 1617

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I hereby certify this correspondence is being deposited with the United States Postal Service as first class mail, postpaid in an envelope, addressed to: Assistant Commissioner for Patents, Washington, D.C. 20231 on October 25, 2000

Dated: 10/25/00 D. Concha

Assistant Commissioner for Patents
Washington, DC 20231

DECLARATION UNDER 37 C.F.R. §1.132

Sir:

I, CHARANJIT R. BEHL, declare and say:

1. I received a Ph.D. from the University of Michigan in 1979. I was a research faculty member at University of Michigan.

2. I have been on the scientific staff of Nastech Pharmaceutical Company, Inc. since January 1995. Nastech is the assignee of the application identified above.

3. I previously held senior research positions in the Pharmaceutical Research and Development Department of Hoffmann La-Roche, Inc, Nultey, NJ for about fourteen years.

4. During my tenure at Hoffmann La-Roche and as a research faculty member at the University of Michigan, I performed extensive research and product development on various drug delivery systems. I have worked on the optimization of drug delivery via different routes, including nasal, enteral, transdermal (local and systemic), rectal, vaginal and

trans-nail. Most of my research has been focused on the optimization of absorption and stability of "difficult" drugs.

5. I have authored/co-authored well over hundred articles and major meeting abstracts including many book chapters. One of my co-authored articles was awarded the Ebert Prize for best publication in 1989/1990 by the American Pharmaceutical Association (AphA).

6. I have been involved in organizing international workshops, conferences and meetings to address issues pertaining to drug delivery. Currently I am co-chairing a Nasal Drug Delivery Focus Group at the American Association of Pharmaceutical Scientists (AAPS) with a mission to optimize interactions amongst the FDA, industry and academia.

7. I am an active member of the AphA, AAPS and Controlled Release Society. I am a Fellow of the AAPS.

8. I am a co-inventor in the above-referenced patent application.

9. It has been a common teaching in the art that the degree of ionization of a drug influences the drug's ability to permeate a membrane, and correspondingly, the absorption potential of the drug into the blood stream. The degree of ionization of a drug is largely determined by the drug's dissociation constant, the *pKa*, and the pH of the solution in which the drug is dissolved. (The *pKa* of an acid is equal to the pH at which half of the molecules are ionized and half are neutral.) A basic drug would be mostly in its unionized state when dissolved in a solution with a pH that is greater than the *pKa* of the drug. Accordingly, basic drug formulations are believed to be best absorbed from alkaline solutions where pH> *pKa*. In particular, it is a common teaching in the art that basic intranasal drug formulations, are best absorbed into the bloodstream when the basic drug is prepared in a solution having a pH above the dissociation constant of the drug. Morphine is known to be a basic drug with a *pKa* of about 8. Accordingly, it is believed that morphine would be best absorbed when formulated in a basic solution, since in such a formulation most of the morphine would be in its unionized state.

Solutions of morphine sulfate having a formulation pH of greater than about 7.0 are generally thought to allow for good absorption of morphine. For example, approximately 90% of the morphine is in an unionized state (i.e., morphine free base) in morphine sulfate solutions at a pH of approximately 9.0. Accordingly, as would be expected, the morphine from such a solution allows for good absorption. On the other hand, approximately 99% of the morphine is in an ionized state in morphine sulfate solutions with a pH of 6.0. One of ordinary skill in the art would expect that morphine with such a high ionization level would not allow for adequate absorption of the morphine into the bloodstream. However, as shown in the present invention, there surprisingly is a high level of morphine absorption into the bloodstream at pH 6.0. Similar results were shown for morphine sulfate at a pH range of about 3.0 to about 5.0 where over 99% of the morphine is in an ionized state.

10. **Hussain** (USPN: 4,464,378)

The section of the Hussain cited by the Examiner (Col 10, Example 2) would not have taught a skilled artisan an intranasal composition containing morphine with a pH of 4.5.

Firstly, it is not clear if Hussain recites a pH of 4.5 for a morphine sulfate solution at all. Hussain merely states that the procedure described for nalbuphine hydrochloride is substantially repeated for morphine sulfate. The procedure has several steps. One step is adjusting the pH of the nalbuphine hydrochloride to 4.5. However, by stating that the procedure is substantially repeated for morphine sulfate, a skilled artisan would not have been certain if one of the steps to be repeated was to adjust the pH of the morphine sulfate solution to 4.5. In fact, there are several reasons why a skilled artisan would have believed that adjusting the pH of the morphine sulfate solution to a pH of 4.5 is not what Hussain discloses.

For example, Hussain describes his morphine sulfate composition as containing 15mg of morphine sulfate per 0.1ml of water. However, a skilled artisan would not have taken this disclosure seriously. I could not reproduce these experimental results. That is, unlike Hussain describes, the solubility of morphine sulfate in water is **not** 150 mg/ml at any pH. Apropos, the solubility of morphine sulfate at a pH of 4.5 is 53.8 mg/ml.

Moreover, a skilled artisan would not have thought that the disclosure of Hussain describes a morphine sulfate solution at a pH of 4.5. In particular, the procedure outlined by Hussain for nalbuphine hydrochloride clearly cannot be followed to obtain a morphine sulfate solution with a pH 4.5. Hussain teaches to combine 15 grams of nalbuphine hydrochloride with 80 ml of water, and to add enough sodium hydroxide solution to bring the pH of the composition to 4.5. The statement, at Col. 10, Lines 45-49, that this procedure "is *substantially* repeated, except that 15 grams of morphine sulfate are used in place of the nalbuphine hydrochloride" would not have taught a skilled artisan anything about the pH of the resultant morphine composition. More specifically, the resultant pH of morphine sulfate solution would not be 4.5 by following the outlined procedure. According to the Merck Index, morphine sulfate solution has a pH of about 4.8. Thus, the addition of the sodium hydroxide solution to the morphine sulfate solution would bring the pH of the solution up, not down. Therefore, Hussain would not have taught a skilled artisan anything about the pH of the morphine sulfate solution.

11. **Merkus** (U.S. Patents: 5,756,483 and 5,942,251)

A skilled artisan would have been taught from the Merkus patents that a nasally-administered morphine composition at a pH of 6.0 would not be useful.

The nasal administration of pharmaceutical compositions avoids the first pass effect. The first pass effect pertains to the deactivation of drugs via digestive and liver enzymes. Accordingly, one of the objectives in the nasal administration of pharmaceutical compositions, vis-a-vis the oral administration of pharmaceutical compositions, is to avoid the first pass effect and thereby attain higher bioavailability. If this objective is not attained, the value of administering a pharmaceutical composition nasally is diminished.

In particular, in both patents, Merkus states that nasally-administered morphine compositions with a pH of 6.0 have a bioavailability which is substantially lower than the bioavailability for orally-administered morphine. Therefore, a skilled artisan would have been taught to administer morphine compositions orally, not nasally. Accordingly, a skilled artisan would have been taught away from using nasally-administered morphine compositions with a pH of 6.0.

In contrast, the bioavailability of the nasally-administered morphine sulfate composition of the present invention at pH 6.0 is greater than the bioavailability of orally-administered morphine compositions.

12. I hereby declare that all statements made herein of my own knowledge are true, and that all statements made on information and belief are believed to be true. Further that these statements were made with the knowledge that willfully false statements, and the like, so made are punishable by fine or imprisonment or both under Section 1001 of Title 18 of the United States Code, and that such willfully false statements may jeopardize the validity of the application of any patent issued thereon.

10-18-00
Date

Rai Behl
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